Polyhalogenated heterocyclic compounds. Part 48.[1] Synthesis of perfluoroisopropyl-2,2′-bipyridyl derivatives

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Dedicated to Professor Charles Rees on the occasion of his 75th birthday
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Abstract
The synthesis of a highly halogenated 2,2′-bipyridyl system using organometallic methodology is reported.

Keywords: Heterocyclic, organofluorine, bipyridyl, polyhalogenated

Introduction

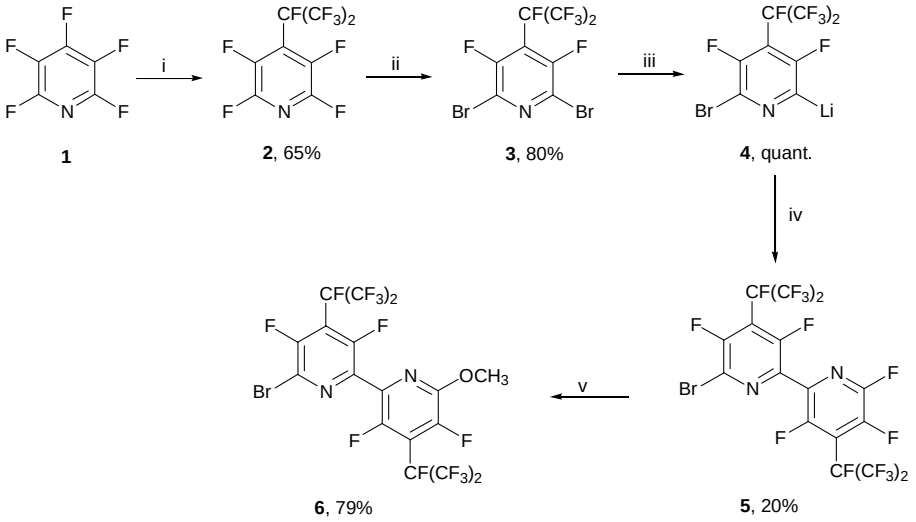
The chemistry of highly fluorinated bipyridyl derivatives remains relatively undeveloped. Earlier work from this laboratory includes synthesis of octafluoro-3,3′-bipyridyl by Ullman coupling of 3-chlorotetrafluoropyridine,[2] halogen exchange reactions, by heating octachloro-bipyridine derivatives with potassium fluoride at high temperature gave octafluoro-2,2′-bipyridyl[3] and electrochemical reduction, involving the generation and coupling of perfluoropyridyl radical anions, gave octafluoro-4,4′-bipyridyl.[4] So far as we are aware, these are the only synthetically realistic methods for the synthesis of these systems that have been reported,[5] together with some studies of factors effecting the orientation of nucleophilic attack in perfluoro-3,3′-bipyridyl.[2]

In this paper, we report the synthesis of a 2,2′-bipyridyl derivative using organometallic methodology.

Results and Discussion

Perfluoroalkylation of pentafluoropyridine **1** was achieved by heating with hexafluoropropene and a catalytic amount of tetrakis(dimethylamino)ethylene (TDAE), following a procedure described earlier.[6] Bromination of perfluoro-4-isopropylpyridine **2** by heating with hydrogen

bromide and aluminium tribromide in an autoclave, proceeded efficiently to give the 2,6-dibromo pyridine derivative **3** in high yield.[1] The subsequent reaction of **3** with *n*-butyl lithium in THF at low temperature afforded the lithio derivative **4** and then addition of one equivalent of the heterocycle **2**, which is highly susceptible to nucleophilic attack, led to 2,2′-bipyridyl derivative **5** in moderate yield. (Scheme 1) However, we have not yet probed the factors that may lead to an increase in the yield of **5**. Characterisation of **5** followed readily from elemental analysis, mass spectrometry and ^{19}F n.m.r.



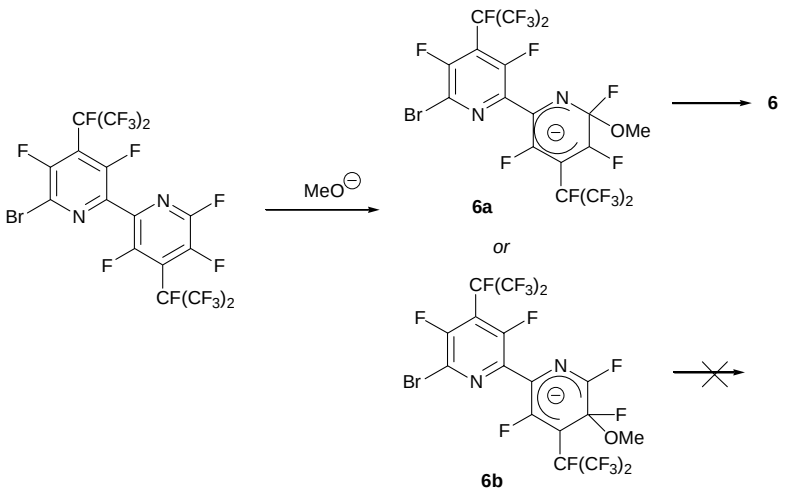
Scheme 1

Reagents and Conditions

(i) CF3-CF=CF2, TDAE, 60oC; (ii) AlBr3 (2.2 equiv.), HBr (2.2 equiv.), 160oC, 48 h; (iii) n-BuLi (1.2 equiv.), THF, -78oC; (iv) 2, -78oC - r.t.; (v) NaOMe, MeOH, reflux, 24h

Bipyridyl derivative **5** is, of course, still very reactive towards nucleophiles. Heating **5** with sodium methoxide lead to the major product **6**, in which the fluorine atom located *ortho* to ring nitrogen was substituted. This was deduced by the disappearance of the diagnostic resonance at –83.1 ppm, assigned to the *ortho* ring fluorine substituent in **4**, in the ^{19}F nmr spectrum.

In principle, nucleophilic attack on the perfluorinated ring could occur at sites both *ortho* and *meta* to the ring nitrogen which would lead to transition states approximating to **6a** and **6b** respectively. (Scheme 2)



Scheme 2

Transition state **6b** would be stabilised by delocalisation of the negative charge into the pyridine ring attached to the carbon atom *para* to the site of nucleophilic attack. However, the product **5** obtained indicates that the *ortho/para* activating influence of ring nitrogen is the dominant factor in these processes leading to preferential *ortho* substitution. Of course, the bromine atom could, in principle, be displaced because this substituent is also located *ortho* to ring nitrogen. However, replacement of the *ortho* fluorine is predominant because, in this case, the 'hard′ oxygen nucleophile preferentially attacks the 'harder′ carbon-fluorine bond rather than the 'softer′ carbon-bromine bond, in line with previous findings.[7]

In summary, methodology for the preparation of bipyridyl derivatives in which a perfluoropyridyl lithium derivative is trapped by another equivalent of a perfluoropyridine has been established and many similar bis-heterocylic systems, synthesised by analogous methodology, can be envisaged.

Experimental Section

General Procedures. All solvents were dried using literature procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a Varian VXR 400S NMR spectrometer with tetramethylsilane and trichlorofluoromethane as an internal standards. Mass spectra were recorded on a Fisons VG-Trio 1000 Spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph using a 25m HP1 (methyl -silicone) column. Elemental analyses were obtained on an Exeter Analytical CE-440 elemental analyser. Melting points and boiling points were recorded at atmospheric pressure unless otherwise stated and are uncorrected. The progress of reactions were determined by either ^{19}F-NMR or gas-chromatography on a Shimadzu GC8A system using a SE30 column. Distillation was performed using a Fischer Spaltrohr MS220 microdistillation apparatus. Column chromatography was

carried out on silica gel (Merck no. 109385, particle size 0.040-0.063nm) and TLC analysis was performed on silica gel TLC plates.
Perfluoro-4-isopropylpyridine **1**, was synthesised by literature procedures. [6]

2,6-Dibromo-3,5-difluoro-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)-pyridine (3). A Hastalloy autoclave was charged with aluminium bromide (34.1 g, 0.13 mol), **2** (19.2 g, 0.06 mol) and hydrogen bromide gas (10.2 g, 0.13 mol). The autoclave was heated at 160˚C for 48 h. After cooling excess hydrogen bromide was neutralised by release into a sodium hydrogen carbonate solution. The autoclave was opened and ice/water was cautiously added to the solid contents. This mixture was then extracted with dichloromethane and the extracts were dried ($MgSO_4$) and distilled under reduced pressure to give *2,6-dibromo-3,5-difluoro-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)-pyridine* **3** (21.6 g, 80%) as a colourless liquid; bp 56˚C (4mmHg); (Found C, 21.8; N, 3.1. $C_8Br_2F_9N$ requires C, 21.8; N, 3.2%); δ_F –75.8 (6F, m, CF_3), -103.7 and –105.8 (2F, br s, F-3), -180.0 (1F, m, C*F*CF_3); δ_C 91.5 (dsept, $^1J_{CF}$ 216, $^2J_{CF}$ 36.0, $CFCF_3$), 114.1 (dt, $^2J_{CF}$ 22.5, $^2J_{CF}$ 13.3, C-4), 119.7 (qd, $^1J_{CF}$ 289, $^2J_{CF}$ 27.1, CF_3), 124.0 – 126.2 (br m, C-2), 148.0 – 155.0 (br m, C-3); *m/z* (EI^+) 443 (M^+, 33%), 441 (M^+, 41%), 439 (M^+, 48%), 343 (11), 341 (11), 324 (24), 322 (48), 320 (27), 212 (15), 193 (18), 162 (32), 124 (20), 69 (100).
2-Bromo-3,5-difluoro-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)-6-lithiopyridine (4). A solution of *n*-butyllithium (3.5 cm^3, 5.5 mmol of 1.6 M solution in hexanes) was added to a solution to **3** (2.0 g, 4.5 mmol) in tetrahydrofuran (25 cm^3) at -78˚C, with stirring, under an atmosphere of dry nitrogen.
2-Bromo-3,5-difluoro-4-[1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl]-6-{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl](2-pyridyl)}pyridine (5). **2** (7.1 g, 22.2 mmol) was added to a solution of **4** as prepared above and the mixture was stirred for 0.5 h at -78˚C, then warmed to room temperature. Water (30 cm^3) was added and the organic components were extracted into dichloromethane. The dichloromethane solution was dried ($MgSO_4$) and evaporated to give a residue which after column chromatography, using hexane and dichloromethane (4:1) as the eluent, gave *2-bromo-3,5-difluoro-4-[1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl]-6-{3,5,6-trifluoro-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl](2-pyridyl)}pyridine* **5** (0.6 g, 20%) as a white solid; mp 68-69.5˚C; (Found C, 29.1; N, 4.2. $C_{16}BrF_{19}N_2$ requires C, 29.1; N, 4.2%); δ_F –75.2 (12 F, m, CF_3), -82.9 and –83.8 (1 F, br m, F-2′), -97.3 and –99.5 (1 F, br m, F-3′), -115.0 and –119.8 (2 F, br m, F-5, 5′), -124.7 and –127.5 (1 F, br m, F-3), -179.6 (2 F, m, C*F*CF_3); *m/z* (EI^+) 662 (M^+, 8%), 660 (M^+, 9%), 69 (100).
2-{6-Bromo-3,5-difluoro-4-[1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl](2-pyridyl3,5,-)} difluoro-6-methoxy-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]pyridine (6). Under an atmosphere of dry nitrogen, sodium metal (0.02 g, 0.8 mmol) was added to methanol (20 cm^3) and stirred until hydrogen evolution was complete. **5** (0.5 g, 0.8 mmol) was added to the solution which was stirred at reflux temperature for 24 h. Water (30 cm^3) was added and the organic components were extracted into dichloromethane. The dichloromethane solution was dried ($MgSO_4$) and evaporated to give a residue which after column chromatography, using hexane

and dichloromethane (4:1) as the eluent, gave *2-{6-bromo-3,5-difluoro-4-[1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl](2-pyridyl)}{3,5,-difluoro-6-methoxy-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]pyridine* **6** (0.4 g, 79%) as a white solid; mp 79.8-81.6˚C (Found: C, 30.3; H, 0.4, N, 4.2. $C_{17}H_3BrF_{18}N_2O$ requires C, 30.3; H, 0.5; N, 4.2%); δ_H 4.0 (s, CH_3); δ_F –75.4 (12 F, m, CF_3), -97.3 and –99.5 (1 F, br m, F-3), -115.2 and –119.6 (2 F, m, F-5,5′), -124.7 and –127.1 (1 F, m, F-3′), -179.9 (2 F, m, C*F*CF_3); *m/z* (EI^+) 674 (M^+, 48%), 672 (M^+, 56%), 659 (11), 657 (11), 469 (16), 467 (17), 343 (11), 293 (15), 248 (20), 69 (100).

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References

1. Chambers, R. D.; Hoskin, P. R.; Sandford, G.; Yufit, D. S.; Howard, J. A. K. *J. Chem. Soc., Perkin Trans 1* **2001**, 2788.
2. Chambers, R. D.; Lomas, D.; Musgrave, W. K. R. *J. Chem. Soc.*, *C* **1968**, 625.
3. Chambers, R. D.; Lomas, D.; Musgrave, W. K. R. *Tetrahedron* **1968**, *24*, 5633.
4. Chambers, R. D.; Musgrave, W. K. R.; Sargent, C. R.; Drakesmith, F. G. *Tetrahedron* **1980**, *37*, 591.
5. Brooke, G. M. *J. Fluorine Chem.* **1997**, *86*, 1.
6. Chambers, R. D.; Gray, W. K.; Korn, S. R. *Tetrahedron* **1995**, *51*, 13167.
7. Chambers, R. D.; Hall, C. W.; Hutchinson, J.; Millar, R. W. *J.Chem. Soc., Perkin Trans 1* **1998**, 1705.

